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Lung cancer and its association with chronic obstructive pulmonary disease: update on nexus of epigenetics

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Abstract

Purpose of review—Chronic obstructive pulmonary disease (COPD) and lung cancer are the leading causes of morbidity and mortality worldwide. The current research is focused on identifying the common and disparate events involved in epigenetic modifications that concurrently occur during the pathogenesis of COPD and lung cancer. The purpose of this review is to describe the current knowledge and understanding of epigenetic modifications in pathogenesis of COPD and lung cancer.

Recent findings—This review provides an update on advances of how epigenetic modifications are linked to COPD and lung cancer, and their commonalities and disparities. The key epigenetic modification enzymes (e.g. DNA methyltransferases – CpG methylation, histone acetylases/deacetylases and histone methyltransferases/demethylases) that are identified to play an important role in COPD and lung tumorigenesis and progression are described in this review.

Summary—Distinct DNA methyltransferases and histone modification enzymes are differentially involved in pathogenesis of lung cancer and COPD, although some of the modifications are common. Understanding the epigenetic modifications involved in pathogenesis of lung cancer or COPD with respect to common and disparate mechanisms will lead to targeting of epigenetic therapies against these disorders.

Keywords

chromatin; chronic obstructive pulmonary disease; epigenetics; histones; lung cancer; methylation

Introduction

The incidence of chronic obstructive pulmonary disease (COPD) and lung cancer is among the major medical challenges, and the current research is focused on understanding the pathogenesis and therapeutic approaches of these disorders. Environmental risk factors and (epi)-genetic predisposition contribute to the development of both diseases. COPD is shown to increase the susceptibility for lung tumorigenesis up to four-fold to five-fold [1]. Furthermore, there is a shared mechanism driving the progression of both diseases [2] in which cigarette smoke-mediated oxidative stress has a major impact on the epigenome

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leading to epigenetic modifications, compared to genetic (inherited germline sequence-based) susceptibility which occurs only approximately 1% of smokers. The current research is focused on identifying the common and disparate events involved in epigenetic modifications that concurrently occur between COPD and lung cancer. This review focuses on current knowledge of specific processes or molecules that are at the nexus of COPD and lung cancer, with particular emphasis on shared or common and disparate epigenetic alterations via histone modification enzymes, but not by other regulatory elements, such as microRNAs.

Chromatin remodeling or epigenetic modifications

Cigarette smoke is the cause of 80–90% cases of COPD and lung cancer because, in part, of its ability to induce oxidative stress and inflammation either directly by inhaled oxidants or influx of inflammatory cells in the lung. Oxidative stress and inflammatory response eventually then alter the redox status of the cells leading to destabilization of the genome culminating in epigenetic modifications.

Histone tails are modified by an extensive group of nonhistone chromatin-associated proteins called chromatin-modifying enzymes, which exist in cells as multicomponent protein complexes that are frequently recruited to chromatin in association with DNA-bound transcription factors [3]. Various covalent post-translational modifications (PTMs) in histones and associated regions of DNA play vital roles in genomic functions by binding specific transcription factors and co-activators, which in turn serve to alter the structural property of chromatin [4].

The chromatin modification enzymes are classified into several enzyme classes based on their functions: acetylation by histone acetyltransferases (HATs), deacetylation by histone deacetylases (HDACs), methylation by histone methyltransferases (HMTs), and demethylation by histone demethylases (HDMs) (Fig. 1). The resulting PTMs may act alone or in concert to facilitate the activation or repression of chromatin-mediated gene expression for inflammatory mediators, genes for cell cycle arrest, apoptosis, senescence, anti-oxidants, growth factors, and tumor suppressor genes involved in COPD and lung cancer [5,6]. The possible link for specific epigenetic modifications on genes involved in the above events in different disease phenotypes might be due to the environment and alterations in gene expression patterns [7], which occurs in patients with COPD and lung cancer.

CpG methylation: role of DNA methyltransferases

Lung cancer exhibits profound alterations in chromatin structure. Genome-wide DNA demethylation with site-specific hypermethylation occurs in the bronchial epithelium of smokers, lung cancer cells, and lung tumors [8,9,10••]. Clinical data from patients with lung cancer demonstrated that the overexpression of DNA methyl-transferase 1 (DNMT1), which catalyzes methylation of DNA in CpG islands, was associated with p53 mutation and increased expression of specificity protein 1 (Sp1) [11]. Nicotine-derived nitrosamine ketone (NNK)-induced activation of DNMT1 causes epigenetic alterations, such as hypermethylation of promoters of multiple tumor suppressor genes leading to lung tumorigenesis and poor prognosis, thus providing an important link between tobacco smoking and lung cancer [12•].

There are conflicting reports in the literature regarding the relationship between gene-specific DNA methylation and smoking [13]. Studies in methylation from lung tissue of non-small cell lung cancer (NSCLC) patients showed no significant association between smoking history and promoter hypermethylation in the genes *APC1* [14], *DAPK* [15], and *p16* [16]. On the contrary, significant associations between promoter hypermethylation and

with smoking history has been reported in NSCLC patients in *CDKN2A* [17–19], *HIC1* [20], *HtrA3* [21], and *CHFR* [22].

There are several reports that describe promoter hypermethylation and associated gene-silencing of various genes in lung cancer [8]. Several of these studies likely include a subset of COPD patients; however, they are not typically studied separately to identify COPD-specific signals. The identification of CpG methylation events in COPD as precursor events in lung cancer could have predictive clinical significance. It is plausible that genes which are involved in COPD pathways would represent commonalities in their regulation, including possible silencing via CpG hypermethylation. Examples of such candidate genes that have been reported as hypermethylated in lung cancer or COPD are listed in Table 1 [23•,24–30,31•].

Histone acetyltransferases

Cigarette smoke induces acetylation of histone H3 in macrophages and in lung of humans and rodents, which implies that histone acetylation plays a vital role in chromatin remodeling, and is subsequently associated with sustained lung inflammatory response in patients with COPD [32–35]. Global HAT activity does not change despite acetylation of histones H3 and H4 on specific lysine residues in response to cigarette smoke in mouse lungs [32,35], and in lungs of smokers and COPD patients [34,36]. CREB-binding protein (CBP) and p300 are the key transcriptional co-activators regulated by mitogen-activated protein kinase (MAPK), and possess intrinsic HAT activity [37–39]. A recent study demonstrated the role of protein kinase C zeta in cigarette smoke or reactive aldehydes and bacterial lipopolysaccharide (LPS)-induced lung inflammation via CBP-mediated acetylation of RelA/p65 causing histone phosphorylation and acetylation on promoters of pro-inflammatory genes [40•]. Cigarette smoke-derived oxidants activate IKKα and phosphorylate RelA/p65 (Ser276) and histone H3 (Ser10), and acetylate histone H3 (Lys9) by interacting with RelA/p65 and CBP/p300 [35,41].

CBP gene alterations include mutations and deletions detected in lung cancer cell lines, as well as in surgical specimens from patients with lung cancer, suggesting the role of CBP in the tumorigenesis and/or progression of a subset of lung cancers [42]. Horwitz *et al.* [43] reported that adenovirus E1A interacts with histone modification enzymes possibly via CBP/p300, forming a basis for global epigenetic modifications that leads to cellular transformation particularly seen in lung of patients with COPD and lung cancer. Hence, development of small molecule inhibitors against various HATs including co-activators (p300, CBP, PCAF, and GCN5) may be potential targets for pharmacological and therapeutic applications to treat COPD and lung cancer [44,45] (Table 2).

Histone deacetylases

Reduction of HDACs, particularly HDAC2, is associated with steroid resistance in COPD. The levels and activities of histone deacetylases, particularly HDAC2 [36,46,47] and sirtuin 1 (SIRT1), are reduced in lungs and alveolar macrophages of patients with COPD [48,49]. A recent study showed the role of the HDAC2–Nrf2 axis on steroid resistance to control lung inflammatory response [50•]. Reduction in HDAC2 levels or activity leads to acetylation of NF-κB and glucocorticoid receptor α, resulting in abnormal inflammatory response and steroid resistance in lungs of patients with COPD [51] (Table 2). Restoring HDAC2/SIRT1 levels or activities will have a significant impact on steroid efficacy, thus inhibiting chronic inflammatory response in COPD [52,61,62].

In contrast, alterations in expression and somatic gene mutations encoding HDACs have been linked to tumor progression and aberrant transcription of key genes regulating

important cellular functions, such as cell proliferation, cell cycle regulation, and apoptosis [63]. Aberrant expression of HDACs is implicated in the progression of tumorigenesis as well as in metastatic phenotypes. Examples of this include increased HDAC1, and decreased HDAC5 and HDAC10 expression correlated with advanced stages of disease with adverse outcome in lung cancer patients [53] (Table 2). Another study showed the involvement of HDAC6 in epithelial–mesenchymal transition of lung cancer cell metastasis *in vitro* via the TGF-β SMAD3 signaling cascade [64]. Recently, Haberland *et al.* [65] using a genetic approach found that deletion of single class I HDAC is not sufficient to cause cell death but both HDAC1 and HDAC2 play redundant and essential roles in the survival of tumor cells, as well as in DNA-damage response by promoting double-strand break repair. This provides deeper insight into the radio-sensitizing effects of a combination of HDAC inhibitors (HDACi) that are under development for cancer therapies [66••]. Further studies are required to understand the mechanism of such disparity in HDAC regulation in lung cancer and COPD.

Histone methyltransferases

HMTs are deregulated in several types of cancers and thus affect the global methylation levels. Methylation at H3K4, H3K36, and H3K79 is linked to gene activation, whereas H3K9, H3K27, and H3K20 methylation is associated with gene repression [67]. Loss of trimethylation of histone H3K20 in selective tumor cells [68] and in-vivo demonstration of HMT SUV39H deficiency sensitizes mice to tumorigenesis [54]. These findings provide evidence that alterations in histone methylation may play a vital role in tumor onset and/or progression [69].

Epigenetic silencing of *CXCL14* by histone methylation in sputum samples of early-stage asymptomatic lung cancer patients were associated with increased (2.9-fold) risk of lung cancer compared to the controls [70]. Protein arginine *N*-methyltransferases (PRMTs), such as PRMT1 and PRMT6, have been identified to play a role in carcinogenesis [55], but no information is available in lung cancer. Liu *et al.* [71] established an in-vitro system to examine the effects of cigarette smoke-induced cancer-associated epigenomic alterations, such as decreased levels of H4K16ac and H4K20me3, but increased relative levels of H3K27me3 coincided with decreased DNMT1 and increased DNMT3b expression in cultured normal human small airway epithelial cells and cdk-4/hTERT-immortalized human bronchial epithelial cells. These features help to delineate some early epigenetic mechanisms regulating gene expression during lung cancer development [56,71] (Table 2).

Histone demethylases

The HDMs are classified into two kinds, such as lysine-specific demethylase 1 (LSD1) and Jumonji C (JmjC) domain family proteins involved in the regulation of gene expression [72]. Aberrant expression of HDMs is manifested during the course of tumor initiation and progression [73]. The role of HDMs in lung cancer and COPD is not known though hypoxia, which is known to occur in the tumor microenvironment and in lungs of patients with COPD, alters HDMs, such as JMJD1A, JMJD2B, and JARID1A [57•–59•].

A recent report showed the involvement of another HDM, JARID1B (KDM5B), in growth of cancer cells through the E2F/RB1 cell cycle regulation pathway in various cancer cell lines. Microarray analysis and immunohistochemistry revealed an elevated expression of KDM5B in lung tumor tissues of both NSCLC and SCLC compared to non-neoplastic tissues, suggesting the role of JARID1B overexpression in lung carcinogenesis [60]. Thus, the inhibition of histone demethylase represents a viable tool in epigenetic therapeutics potentiating the activity of hypomethylating agents [74] (Table 2).

Conclusion

Cigarette smoke-mediated alterations in histone modification enzymes and molecules are linked to molecular and cellular functions such as post-translational modifications of histones, gene expression of inflammatory mediators, cell cycle arrest, apoptosis, senescence, autophagy, unfolded protein response, antioxidants or stress response, growth factors, and tumor suppressor genes, and DNA replication, recombination, and repair. Understanding the epigenetic mechanisms that influence the human genome based on the effects from the environment results in transcriptional activation of specific genes, at a specific time point, in specific cell types or organs are the important areas of further research in development and progression of COPD and lung cancer. This understanding will lead to a deeper insight into identifying the potential link between CpG methylation, chromatin modification enzymes, and microRNAs (which modulate certain DNMTs) implicated in the pathogenesis of cigarette smoke or environmental stress-mediated chronic lung diseases such as COPD and lung cancer [75]. Further studies on the molecular mechanisms underlying histone modification enzymes involved in chromatin modification will provide insights into specific therapeutic targets based on either common and/or disparate mechanisms and devising treatment strategies based on epigenetics against lung cancer and COPD.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 294–295).

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Key points

- This review highlights the importance of epigenetic alterations mediated by chromatin modification enzymes that are at the nexus of chronic obstructive pulmonary disease (COPD) and lung cancer.
- Post-translational modification of histones facilitates activation or repression of genes linked to pathogenesis of COPD and lung cancer.
- DNA methyltransferases, causing hypermethylation of genes and promoters, histone acetyltransferases and histone deacetylases play a crucial role in opening and closing the chromatin to modulate gene expression.
- Histone methyltransferases and histone demethylases are vital to maintain the structure of hetero-chromatin, which is implicated in pathogenesis of COPD and lung cancer.
- Understanding the signaling molecules and pathways involved in epigenetic modifications will provide a new insight to help identify therapeutic targets and devise therapies based on epigenetics against these disorders.

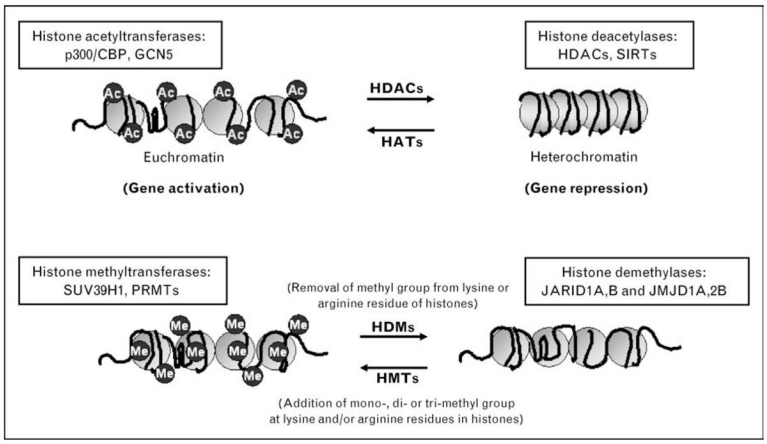

Figure 1.

Major chromatin modification enzymes involved in posttranslational modification of histones in chronic obstructive pulmonary disease and lung cancer

Table 1

Examples of candidate genes methylated and their functions in chronic obstructive pulmonary disease and lung cancer

Gene name	Function	References
IL-12Rβ2, *Wif-1*	Cell transduction/signaling genes involved in the development of COPD-related NSCLC	[23•]
KEAP1	Redox-sensitive transcription factor regulates antioxidant genes	[24]
SERPINB5	Serpin peptidase inhibitor	[25]
TIMP3, *TIMP4*	Tissue inhibitor of metalloproteinase 3 and 4, involved in degradation of extracellular matrix	[26]
DUOX1, *DUOX2*	Dual oxidases: hydrogen peroxide production and host defense in airways	[27]
GSTP1	Glutathione-S-peroxidase, local detoxification and protective function in lung	[28]
CYGB	Detoxification of reactive species	[29]
ECSOD	Maintenance of normal redox homeostasis in the lung	[30]
P16, *GATA4*	Cell transduction/signaling	[31•]

COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer.

Table 2

Chromatin modification enzymes, associated histone modifications and their role in chronic obstructive pulmonary disease and cancer

Enzymes	Cigarette smoke/COPD	Cancer	Role in cigarette smoke/COPD and cancer	References
DNA methyltransferase				
DNMTs	DNMT1↓, DNMT3b↑	DNMT1↑, H4K16ac↓, H4K20me3↓, H3K27me3↑	Regulate gene expression in lung cancer development	[10••,12•]
Histone acetyltransferases				
CBP/p300	H3S10↑, H3K9ac↑	H3K9ac↓, H3K56ac↓	Chromatin remodeling and sustained inflammatory response in COPD. Interaction of E1A and p300 in prostate cancer and cellular transformation. DNA damage response in human cell lines	[32,39,40•,42,45]
GCN5	–			
Histone deacetylases				
HDACs	HDAC2↓, SIRT1↓	SIRT1↓, HDAC1↑, HDAC5↓, HDAC10↓	Abnormal inflammatory response and steroid resistance. Aberrant expression of HDACs in tumor progression	[36,46–49,50•,51–53]
Histone methyltransferases				
SUV39H	–	SUV39H↓	Impairs heterochromatin and genome stability	[54]
PRMTs	–	PRMT1↑, PRMT6↑	Role in growth and regulation of cancer cells	[55,56]
Histone demethylases				
JMJD2B	–	JMJD2B↑	Hypoxia dependent HIF-1α and ERα signaling regulates histone methylation in hypoxia. Hypoxia-mediated global activation of H3K4me3 involved in growth of cancer cells through E2F/RB1 cell cycle regulation pathway in NSCLC and SCLC	[57•]
JMJD1A	–	–		[58•]
JARID1A	–	H3K4me3↑		[59•]
JARID1B		JARID1B↑		[60]

COPD, chronic obstructive pulmonary disease; DNMT, DNA methyltransferase; HDAC, histone deacetylase; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.